DECLARATION OF DR. KANWALJETT S. ANAND

I am Dr. Kanwaljeet S. Anand, M.B.B.S., D. Phil, FAAP, FCCM, FRCPCH, who files this Declaration under penalty of perjury. I know from my education, training, and experience that the foregoing facts are true and correct and to the extent I have stated opinions, the basis thereof is also stated:

1. I am a pediatrician specialized in the care of critically ill newborns and children. I serve as a tenured Professor of Pediatrics, Anesthesiology, Perioperative & Pain Medicine at Stanford University School of Medicine, and as Director of the Pain/Stress Neurobiology Laboratory at the Maternal & Child Health Research Institute. For more than 30 years, I have conducted intensive research and study of the development of pain/stress in human newborns, their development during early childhood, and long-term outcomes. I have authored 316 scientific publications (125 in the last 10 years), edited 9 books and received numerous professional awards. My true and correct Curriculum Vitae is attached.
2. I am personally familiar with Opioid Use Disorder (OUD) in pregnancy and Neonatal Abstinence Syndrome (NAS) and have reviewed all materials referenced below along with the Statement of Facts Supporting the Motion for Preliminary Injunction and the Exhibits referenced therein.
3. The medical journal articles attached as exhibits are peer-reviewed or are issued by governmental agencies and reliable treatises/reports on which I and others in healthcare routinely rely.
4. Neonatal abstinence syndrome (NAS) is a clinical diagnosis, and a consequence of the abrupt discontinuation of chronic fetal exposure to opioids that were used or abused by the mother during pregnancy. NAS is a generalized multisystem disorder, which predominantly involves

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the central and autonomic nervous systems, as well as the gastrointestinal tract. Neonatal withdrawal due to prolonged maternal opioid use may be severe and intense. Although NAS is rarely fatal, it can cause significant illness and often results in prolonged hospital stays with the potential for abnormal brain development and future disability. Opioid exposures in early pregnancy can be associated with brain damage and/or congenital defects or deformities, some of which can be improved by surgical or other interventions.

5. Opioid Use Disorder (OUD) is defined in the DSM-5 as a problematic pattern of opioid use leading to clinically significant impairment or distress. OUD has also been referred to as "opioid dependence" or "opioid addiction."

6. In my opinion, the proposal sought by the Motion for Preliminary Injunction is medically and scientifically reasonable because prevention and education are the only feasible means of preventing in-utero opioid exposure. This is because since the introduction of Oxycontin and other similar synthetic and time-released-synthetic opioids the use of prescription opioid medications tremendously increased in the US population as a whole and particularly among women, including those with the ability to become pregnant. Epidemiological studies show that increasing numbers of women are taking opioids during pregnancy, associated with an increasing potential for NAS and OUD-related effects in babies.

7. Since 1995, as is well-documented in the literature, increasing numbers of women within the reproductive age group are using licit and illicit opioids. This too increases the potential for NAS and OUD injuries to babies since pregnancy can occur at any time during the opioid treatment. Patients taking licit or illicit opioids can become addicted and there is a recognized correlation between licit and illicit opioid abuse and addiction. At all ages, but particularly among adolescents or young adults, many patients report first taking prescription opioids before progressing to illicit opioids. Medical standards of care involving opioid use in pregnant

women are evolving. The date on which every healthcare provider and patient will understand and appreciate the danger of opioids to fetal development is unknown. It is likely that the prevalence of opioid use changed after the admission of Oxycontin and similar drugs on the market. Since medical information concerning these medications has grown and addiction and abuse from them is now recognized, the standard of care is still evolving. As a fundamental matter, opioid addiction and in-utero opioid-related injuries are difficult to treat. The efforts and costs associated with the proposed Preliminary Injunction, requiring negative urine pregnancy tests and coupled with the seven-day limitation, is consistent with other drugs known to cause fetal injury, such as Accutane. My office, like doctors' offices around the country, routinely deals with the administrative tasks associated with filling a prescription, which are already part of the prescription process. Urine pregnancy tests are inexpensive, readily available, and reliable; they are routinely administered in hospitals, clinics, or other testing facilities before a woman undergoes certain procedures and tests.

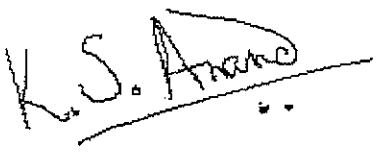
8. Prescription opioid use in pregnancy is strongly associated with neonatal complications.
9. Opioid use can disrupt fetal brain development at any stage during pregnancy, except the first 10-14 days after conception
10. Risks of sudden infant death syndrome (SIDS) in preterm infants with prenatal opioid exposure are increased because of the changes in normal infant sleeping patterns, depressed respiration or respiratory responses to hypoxia (low oxygen levels).
11. Preschool aged children, exposed to opiates, are known to the experience one or more of the following symptoms: mental and motor deficits, cognitive delays, hyperactivity, impulsivity, attention deficit disorder, behavior disorder, aggressiveness, poor social engagement, failure to thrive (socially), and short stature.

12. School-age children exposed to opiates may experience one or more of the following cognitive/behavioral deficits: verbal impaired performance, impaired reading and arithmetic skills, for mental and motor development, memory and perception problems, attention deficit hyperactivity disorder, developmental delays, speech problems, language disorders, impaired self – regulation, school absence, reduced executive functions and behavioral regulation, abnormal responses to stressful situations, poorly developed confidence or efficacy, impaired task performance, depressive disorder, and substance abuse disorder.

13. A recent animal study concluded that the opioid exposure to the developing fetal brain may cause epigenetic modifications that makes addiction in that individual more likely. This modification, no matter the sex of the exposed fetus, is thought to pass on in their genetic material to their offspring.

14. The number of NAS/OUD children in the U.S. is estimated by the CDC to be hundreds of thousands. But when mothers stop taking opioids during pregnancy the fetus may go through in utero withdrawal, so those babies cannot be counted. In addition, only 28 states report NAS/OUD births.

I declare under penalty of perjury that the statements in this declaration are true and correct to the best of my knowledge, information, and belief.
Executed the 27th day of March 2019



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DN: cn=Sunny Anand, o=Stanford University, ou=School of Medicine, Department of Pediatrics, email=anandam@stanford.edu, c=US
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Morphine induces apoptosis of human microglia and neurons

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Abstract

Apoptosis plays a critical role in normal brain development and in a number of neurodegenerative diseases. Recently, opiates have been shown to promote apoptotic death of cells of the immune and nervous systems. In this study, we investigated the effect of morphine on apoptosis of primary human fetal microglial cell, astrocyte and neuronal cell cultures. Exposure of microglia and neurons to 10^{-6} M morphine potently induced apoptosis of these brain cells (approximately fourfold increase above untreated control cells). In contrast to microglia and neurons, astrocytes were completely resistant to morphine-induced apoptosis. Concentration–response and time-course studies indicated that neurons were more sensitive than microglia to morphine's effect on apoptosis. Naloxone blocked morphine-induced apoptosis suggesting involvement of an opiate receptor mechanism. Potent inhibition (>70%) of apoptosis by an inhibitor of caspase-3 as well as co-localization of active caspase-3 and DNA fragmentation in microglia or neurons treated with morphine indicated that caspase-3 is involved in the execution phase of morphine-induced apoptosis. The results of these in vitro studies have implications regarding the potential effect of opiates on fetal brain development and on the course of certain neurodegenerative diseases.

Keywords: Apoptosis; Astrocytes; Microglia; Morphine; Neurons; Opiate receptors

1. Introduction

Apoptosis is a genetically determined mechanism of programmed cell death that can be triggered by a variety of internal and external stimuli. At one end of the age spectrum, apoptosis plays a critical role in the development of the normal nervous system and at the other end, apoptosis appears to be involved in brain cell death accompanying neurodegenerative disorders, such as Alzheimer's disease and Parkinson's disease (Honig and Rosenberg, 2000; Martin, 2001; Sastry and Rao, 2000; Yuan and Yanker, 2000). Apoptosis is also a pathologic feature of amyotrophic lateral sclerosis, ischemic brain injury, certain inflammatory diseases of the brain and central nervous system (CNS) infections, such as human immunodeficiency virus (HIV)-associated dementia (Kaul et al., 2001). Studies of the complex molecular and biochemical mechanisms involved in apoptosis have revealed that this pathway to cell destruction commonly involves the sequential activation of a cascade of intracellular cysteine proteases termed caspases (Cohen, 1997; Hengartner, 2000; Nicholson, 1999). Of the over one dozen caspases thus far identified in humans, caspase-3 plays a pivotal role in the terminal or execution stage of apoptosis (Nicholson, 1999).

Given the enormous importance of apoptosis in physiological and pathologic processes, it is not surprising that cells of the immune system have also been the subject of intensive study (Scaffidi et al., 1999). Because depletion of $CD4^+$ lymphocytes plays a critical role in the development of the acquired immunodeficiency syndrome, HIV-related apoptosis has captured major research attention (McCune, 2001). Spurred largely by an interest in the potential role of opiates in the immunopathogenesis of HIV, several research groups have demonstrated that lymphocytes and macrophages possess μ-, κ-, and δ-opioid receptors, the activation of which can result in suppressed cell function (McCarthy et al., 2001). Studies in our laboratory have focused on microglial cells, the resident macrophages of the brain, which express μ-opioid receptors (MOR) (Chao et al.,

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Do maternal opioids reduce neonatal regional brain volumes? A pilot study

Article *in* Journal of Perinatology - December 2014
DOI: 10.1038/jp.2014.111

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CMCS Informational Bulletin

Date: June 11, 2018

From: Timothy B. Hill, Acting Director

Subject: Neonatal Abstinence Syndrome: A Critical Role for Medicaid in the Care of Infants

This Informational Bulletin provides states with considerations when designing approaches to treatment of infants with Neonatal Abstinence Syndrome (NAS), including Medicaid coverage options and limitations. It contains a summary of some current studies on such treatment, which suggest possible strategies states may want to consider in building effective coverage programs. It further discusses ways in which Medicaid can support the mothers, fathers, and caregivers of the infants in providing care that can improve health outcomes for their infants with NAS.

Background

Neonatal Abstinence Syndrome (NAS) is a constellation of symptoms in newborn infants exposed to any of a variety of substances in utero, including opioids.[1] Clinically significant neonatal withdrawal most commonly results from exposure to opioids, but symptoms of neonatal withdrawal have also been noted in infants exposed to antidepressants, anxiolytics, and other non-opioids.[2] NAS is not characterized as an addiction or substance use disorder; rather it is a medical condition resulting in a physiologic response to the infant's exposure to cessation of the opioid or other substance the mother was using.[3]

NAS is a significant and rapidly growing public health concern. It is directly related to the opioid crisis facing this country. The incidence of NAS in the United States increased nearly five-fold between 2000 and 2012[4] from a rate of 1.2 per 1,000 hospital births per year in 2000 to 5.8 per 1,000 hospital births per year in 2012, reaching a total of 21,732 infants diagnosed with NAS in

[1] Wiles JF, Isemann B, Ward LP, Vinks AA, Akinbi H. "Current Management of Neonatal Abstinence Syndrome Secondary to Intrauterine Opioid Exposure." J Pediatr 2014 165:440-6 DOI:10.1016/jpeds 2014.05.010.
[2] Kocherlakota P, "Neonatal Abstinence Syndrome." Pediatrics 2014:134e:e547 (2014) DOI:10.15242/peds.2013-3524
[3] Kocherlakota P, "Neonatal Abstinence Syndrome." Pediatrics 2014
[4] Patrick SW, Davis MM, Lehman CU, Cooper WO "Increasing Incidence and Geographic Distribution of Neonatal Abstinence Syndrome: United States 2009-2012."J Perinato,2015 35, 667, http://dx.doi.org/10.1038/jp.2015.63

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